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APPELLANTS' BRIEF		
Address to: Box Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket	UCAL142CON
	First Named Inventor	N.B. Freimer
	Application Number	08/976,560
	Filing Date	November 24, 1997
	Group Art Unit	1655
	Examiner Name	L. Arthur
	Title	*Methods for treating bipolar mood disorder associated with markers on chromosome 18p*

Sir:

This Brief is filed in support of appellants' appeal from the Examiner's Final Rejection dated April 24, 2001. No claims have been allowed, and claims 1-12 and 25-27 are pending. All claims are appealed. A Notice of Appeal was filed on October 10, 2001, making this Appeal Brief due on December 10, 2001. A Petition and fee for a one-month Extension of Time is filed herewith, making this Appeal Brief due on January 10, 2002. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

Permission to charge the deposit account in the amount of $710.00 is enclosed to cover the $320.00 required per 37 C.F.R. §1.17(c) for filing appellants' brief, the $280.00 for the Request for Oral Hearing, and the $110.00 for the extension of time. In the unlikely event that the check and/or transmittal papers are separated from this document and/or other fees or relief are required, appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number UCAL142CON.

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REAL PARTY IN INTEREST

The inventors named on this patent application are Nelson B. Freimer, Lodewijk Sandkuijl, Pedro Leon, Victor I. Reus, M. Escamilla, L. Alison McInnes, Susan K. Service, Erich M. Flynn, and Edward M. Domengeaux. The inventors assigned their entire rights to the invention to The Regents of the University of California and the University of Costa Rica. The Regents of the University of California granted a license to Millennium Pharmaceuticals, Inc.

RELATED APPEALS AND INTERFERENCES

The instant application is not a subject of any concurrent appeal or interference proceeding.

STATUS OF THE CLAIMS

This application is a continuation of U.S. Patent Application Serial No. 08/916,683, filed August 22, 1997 (now abandoned), which application claims the benefit of priority of U.S. Provisional Patent Application Serial No. 60/023,438, filed August 23, 1996.

Claims 1-16 were originally filed.

In the amendment filed on October 25, 1999, responsive to the July 28, 1999 Office Action, claim 14 was canceled without prejudice to renewal, claims 1-7, 9-11, 13, 15, and 16 were amended, and new claims 17-24 were added. As a result, claims 1-13 and 15-24 were pending.

In the amendment filed on March 17, 2000, responsive to the January 20, 2000 Office Action, claims 13, 15, and 16 were canceled without prejudice to renewal, and claims 4, 8-11, 17, 20, and 24 were amended. As a result, claims 1-12 and 17-24 were pending.

In the amendment filed on October 30, 2000, responsive the June 28, 2000 Office Action, claims 17-24 were canceled without prejudice to renewal, claims 1, 8, 10, and 11 were amended, and claims 25-27 were added. As a result, claims 1-12 and 25-27 were pending.

In the amendment filed October 10, 2001, responsive to the April 24, 2001 Office Action, claim 1 was amended.

All of the pending claims 1-12 and 25-27 shown in attached Appendix I remain pending, rejected, and appealed here.

STATUS OF AMENDMENTS

During the course of prosecution, amendments to claims 1-7, 9-11, 13, 15, and 16 were made in the amendment filed on October 25, 1999; amendments to claims 4, 8-11, 17, 20, and 24 were made in the amendment filed on March 17, 2000; amendments to claims 1, 8, 10, and 11 were made in the amendment filed on October 30, 2000. All amendments were entered.

Entry of an amendment to claim 1 was requested in the Amendment After Final filed October 10, 2001. The Advisory Action dated October 25, 2001 indicated that the amendment to claim 1 would be entered.

SUMMARY OF THE INVENTION

The independent claims currently pending are claims 1, 9, 10, 11, and 27. Applicants claim a method of detecting an increased susceptibility to bipolar mood disorder (BP) in an individual (claim 1); a method for detecting the presence of a BP susceptibility DNA polymorphism in an individual phenotypically diagnosed as having BP (claim 9); a method of genetically diagnosing bipolar mood disorder in an individual (claim 10); a method of confirming a phenotypic diagnosis of BP in an individual (claim 11); and a method of detecting the presence of a BP susceptibility polymorphism in an individual (claim 27).

Manic-depressive illness, or bipolar mood disorder (BP) is characterized by episodes of elevated mood (mania) and depression, and is among the most prevalent and potentially devastating of psychiatric syndromes. The most severe and clinically distinctive forms of BP are BP-I (severe bipolar mood disorder) and SAD-M (schizoaffective disorder manic type). An estimated 2-3 million people in the United States are affected by BP-I. Currently, individuals are typically evaluated for BP using clinical criteria set forth in the most current version of the American Psychiatric Association's "Diagnostic and Statistical Manual of Mental Disorders." Typically, subjective interview methods are used to make a clinical diagnosis.

Currently available drugs – including lithium salts, carbamazepine, and valproic acid -- are effective in only about 60-70% of individuals diagnosed with BP-I, and it is impossible to predict which drug treatments will be effective in particular BP-I affected individuals. Commonly, upon diagnosis, affected individuals are prescribed one drug after another until one is found to be effective.

Despite abundant evidence that BP has a major genetic component, until the present invention, no genetic markers were unequivocally linked to BP. In view of the severity of the disorder, and the limitations inherent in a purely phenotypic diagnosis of BP based on clinical criteria, there is a tremendous need for more objective criteria to identify and subtype individuals with BP. Identification of genetic markers (e.g., polymorphisms) that show linkage to BP would assist in identification of individuals susceptible to BP. Furthermore, genetically subtyping individuals with BP would confirm clinical diagnoses, and would allow a clinician to determine an appropriate therapy based on the genotypic subtype.

- The inventors identified a narrow interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP. This identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification. Specification, page 16, line 12 to page 25, line 10.
- The inventors identified specific polymorphisms that are associated with BP, e.g., allele 154 at D18S59, a microsatellite marker polymorphism that associates with BP; and allele 271 at D18S476, another microsatellite marker polymorphism that associates with BP. Specification, page 24, lines 10-29. These polymorphisms associated with BP both in the pedigree and in the population of unrelated individuals. Thus, at least two polymorphisms are unequivocally associated with BP.
- The inventors described how additional polymorphisms within the defined, narrow region can be identified in other BP patients. Specification, page 27, line 22 to page 29, line 29.

- The inventors described how individuals whose BP status is unknown ("test individuals") can be analyzed for the presence of a polymorphism known to be associated with BP. Specification, page 29, lines 23-29.

The present invention provides, for the first time, a localization of a severe BP susceptibility locus to a 300 to 500 kb region of the short arm of chromosome 18 between SAVA5 and ga203 ("the identified region"). The inventors demonstrated the feasibility of genome screening using linkage disequilibrium mapping, using the recently available set of markers covering the genome.

The inventors demonstrated that the identified region is linked to BP. Further, the inventors demonstrated that **specific polymorphisms** within the identified region are linked to BP. The inventors demonstrated that specific polymorphisms within the identified region are linked to BP, **both** in **pedigree** studies and in **population** studies. The localization of a BP susceptibility locus to the identified region, and the identification of specific polymorphisms associated with BP is a major contribution. The inventors have narrowed the region within which the susceptibility locus is contained, from the entire genome to a narrow interval, and have identified specific polymorphisms within the narrow interval, which are associated with BP.

The invention provides a convenient diagnostic tool for clinicians, who typically rely upon standard interview methods to make a diagnosis of BP. Rather than relying solely on subjective interview processes in diagnosing BP, clinicians can take advantage of the present invention to identify BP-susceptible individuals.

ISSUES

There are two issues on appeal, as follows:

I. WHETHER THE INVENTION IS DESCRIBED UNDER 35 U.S.C. §112, FIRST PARAGRAPH.

II. WHETHER THE INVENTION IS ENABLED UNDER 35 U.S.C. §112, FIRST PARAGRAPH.

GROUPING OF THE CLAIMS

Claims 1-12 and 25-27 are method claims and are argued as a group.

ARGUMENTS

The arguments portion of this Brief is divided into two sections. The first section describes appellants' understanding of the Examiner's rejections. The second section specifically addresses the two issues outlined above relating to the written description and support within the specification for the claimed invention under 35 U.S.C. §112, first paragraph.

THE EXAMINER'S REJECTIONS

Claims 1-12 and 25-27 were rejected under 35 U.S.C.§112, first paragraph, as lacking written description. It was the Examiner's position that the specification contains no description of specific polymorphisms in the region between SAVA5 and ga203 on chromosome 18 that are generally indicative of a susceptibility to bipolar mood disorder (BP), because the specification only teaches that in a pedigree analysis the region between SAVA5 and ga203 is over-represented in individuals in the pedigree who have BP.

Claims 1-12 and 25-27 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification allegedly does not enable any person skilled in the art to make and use the invention commensurate in scope with the claims. It was the Examiner's position that the specification does not reasonably provide enablement for a method of detecting an increased susceptibility to bipolar mood disorder by detecting polymorphisms between and inclusive of SAVA5 and ga203 or any of the other recited markers.

APPLICANTS' RESPONSE TO THE REJECTIONS

The rejection of claims 1-12 and 25-27 under 35 U.S.C. §112, first paragraph, is in error.

Applicants have described in great detail:

(1) Identification of a narrow interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP. This identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification. Specification, page 16, line 12 to page 25, line 10.

(2) Identification of polymorphisms, e.g., allele 154 at D18S59, a microsatellite marker polymorphism that associates with BP; and allele 271 at D18S476, another microsatellite marker polymorphism that associates with BP. Specification, page 24, lines 10-29. Thus, a number of polymorphisms are unequivocally associated with BP.

(3) How additional polymorphisms within the defined, narrow region can be identified in other BP patients. Specification, page 27, line 22 to page 29, line 29.

(4) How individuals whose BP status is unknown ("test individuals") can be analyzed for the presence of a polymorphism known to be associated with BP. Specification, page 29, lines 23-29.

Accordingly, the specification provides both adequate written description and enablement to meet the written description and enablement requirements of 35 U.S.C.§112, first paragraph.

I. WHETHER THE INVENTION IS DESCRIBED UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Final Office Action stated that:

(1) the claimed invention is an association between a polymorphism in the region of chromosome 18 between markers SAVA5 and ga203 and BP, and the specification shows by analysis of a large pedigree that linkage disequilibrium exists at the short arm of chromosome 18 between markers SAVA5 and ga203 and that the DNA between these markers is over-represented in individuals with BP;

(2) the specification teaches that several known microsatellite polymorphic markers produce particular allele sizes when hybridized with the region between SAVA5 and ga203 on chromosome 18;

(3) the specification provides no description of specific polymorphisms in this region which are generally indicative of a susceptibility to BP because the specification only teaches that in a pedigree analysis the region between SAVA5 and ga203 on chromosome 18 is over-represented in individuals in the pedigree who have BP; and

(4) absent a written description disclosing a representative number of species of polymorphisms associated with a susceptibility to BP, the specification fails to show that Applicants were in possession of the claimed invention at the time the application for patent was filed.

Before the issue of written description is addressed, a brief discussion of microsatellite marker polymorphisms is provided.

Comments regarding microsatellite marker polymorphisms

Microsatellite markers are a widely accepted polymorphisms used for genotyping, and for identifying linkages between specific microsatellite marker allele sizes and disease. Microsatellite marker allele sizes are polymorphisms. Microsatellite markers, also known as Simple Sequence Length Polymorphisms (SSLPs), are unique stretches of DNA that contain very short, simple-sequence repeats. Each microsatellite marker is made up of a variable number of di-, tri-, or tetranucleotide repeats at a particular location. Thus, a number of alleles, each of which has a different length, may exist for a given microsatellite marker. These alleles are

inherited in a Mendelian fashion, making it possible to use these polymorphisms as markers for disease and/or disease susceptibility. The fact that microsatellite marker polymorphisms have gained widespread acceptance as markers for disease states is evidenced by the numerous publications in this field. See, for example, SNP and Microsatellite Genotyping: Markers for Genetic Analysis (2000) A.H. Hajeer et al., eds Eaton Press. As discussed in pages 31-32 of an article by S.J. Payne (in Laboratory Methods for the Detection of Mutations and Polymorphisms in DNA, (1997) G.R. Taylor, ed. CRC Press; a copy of page 31-32 was provided as Exhibit 1 along with the amendment, filed March 17, 2000, responsive to the January 20, 2000 Office Action; a copy is provided herewith for convenience), microsatellite markers are highly polymorphic, often have multiple alleles, many with heterozygosity frequencies of 70% or more, and are thus highly informative for genetic analysis.

The instant specification provides adequate written description.

The present claims are directed to a method of detecting an increased susceptibility to BP; a method for detecting the presence of a BP susceptibility DNA polymorphism in an individual phenotypically diagnosed as having BP; a method of genetically diagnosing bipolar mood disorder in an individual; and a method of confirming a phenotypic diagnosis of BP in an individual.

The Final Office Action stated that the specification shows by analysis of a large pedigree that linkage disequilibrium exists at the short arm of chromosome 18 between markers SAVA5 and ga203 and that the DNA between these markers is over-represented in individuals with BP. In reality, the specification shows, by analysis of both a **pedigree** and a **population** of unrelated individuals, that a number of **specific polymorphisms**, namely, specific allele sizes of specific microsatellite markers, are associated with BP. Specification, page 24, line 5 to page 25, line 2. For example, an allele size of 154 base pairs (bp) for microsatellite marker D18S59 is associated with BP; and an allele size of 172 bp for microsatellite marker D18S467 is associated with BP. Specification, page 24, Table I and lines 24-27.

The Final Office Action stated that the specification teaches that several known microsatellite polymorphic markers produce particular allele sizes when hybridized with the region between SAVA5 and

ga203 on chromosome 18. However, a careful reading of the specification shows that the way in which the analysis was conducted is as follows. Microsatellite markers were amplified using polymerase chain reaction (PCR), using forward and reverse primers flanking the microsatellite marker. One of the two primers was detectably labeled. PCR amplification of a microsatellite marker yields a DNA fragment that has the same size as the microsatellite marker itself. Specification, page 18, lines 19-27. Thus, no hybridization was conducted. Instead, the sizes of the microsatellite markers were detected. *The microsatellite marker sizes are polymorphisms.*

The Final Office Action further stated that the "specification contains no description of specific polymorphisms in this region which are generally indicative of a susceptibility to bipolar mood disorder because the specification only teaches that in a pedigree analysis the region between SAVA5 and ga203 on chromosome 18 is over represented in individuals in the pedigree who have bipolar mood disorder." Final Office Action, page 10. This statement is incorrect. What the specification shows is that, by analysis of both a **pedigree** and a **population** of unrelated individuals, a number of **specific polymorphisms**, namely, specific allele sizes of specific microsatellite markers, are associated with BP. Specification, page 24, line 5 to page 25, line 2. Thus, in addition to a pedigree analysis, a **population** analysis was conducted of unrelated individuals. The same specific microsatellite marker allele sizes that were shown to be associated with BP by linkage disequilibrium in the pedigree, were also shown to be associated with BP in unrelated individuals. These specific polymorphisms are useful, therefore, to identify individuals who have an increased susceptibility to BP, to genetically diagnose BP, and to confirm a clinical diagnosis of BP.

The Final Office Action further stated that "[a] polymorphism includes point mutations, small deletions, insertions within and around a bipolar disease locus none of which have been described in the specification." Final Office Action, page 10. There is no statutory requirement under 35 U.S.C.§112, first paragraph, for Applicants to show various types of polymorphisms, only that Applicants show a "representative number" of polymorphisms. However, as discussed above, a number of specific polymorphisms, i.e., microsatellite marker alleles, were unequivocally identified as associated with BP.

As discussed above, alleles of a given microsatellite marker differ from one another in length. These differences in length are due to varying numbers of di-, tri-, or tetranucleotide repeats. A difference in the number of repeats may be due to insertions, and/or deletions, and/or point mutations. Accordingly, the identification of the microsatellite marker alleles associated with BP would appear to satisfy the requirement in the Final Office Action for a variety of types of mutations.

The Final Office Action stated that "the specification only described a linkage analysis of known markers in phenotypically diagnosed bipolar [in] families." Final Office Action, page 10. However, as discussed above, while the microsatellite markers were indeed known, the fact that particular alleles, i.e., polymorphisms, of known markers were associated with BP was not previously known. A contribution of the instant invention is the demonstration that particular microsatellite marker alleles (polymorphisms) are associated with BP, and thus serve as genetic markers for a predisposition to BP.

The Final Office Action cited *In re Regents of the University of California v. Eli Lilly* 43 USPQ 2d, 1389-1412, and stated that "the Court held that a generic statement which defines a genus of nucleic acids only by their functional activity (i.e. polymorphisms which are associated with bipolar disease) does not provide an adequate written description of the genus." Final Office Action, page 11. However, Applicants have identified a number of polymorphisms, and described them, not only in terms of their association with BP, but have also provided their sizes. As these are known markers, the sequences are also known and publicly available. Microsatellite markers are repeats of di-, tri-, and tetranucleotides. Thus, a description of their length is an adequate description of the polymorphism.

Furthermore, knowledge of the specific sequence is not required to practice the claimed invention. For example, detection of a microsatellite marker allele (i.e., a microsatellite polymorphism) does not require knowledge of the sequence. As described in the specification, and as noted above, one need only know the sequences flanking a given microsatellite marker to be able to design PCR primers which will, in a PCR reaction, prime the amplification of the microsatellite marker. The size of the PCR product is readily

determined, and it is the size of the microsatellite marker that is indicative of whether it is polymorphic relative to other alleles of the same marker. Thus, one need not determine the sequence of the marker.

The Final Office Action acknowledged that the instant specification describes several polymorphisms that are associated with BP.

The Final Office Action further stated that "[i]n analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure" and "[i]n the instant case, *the specification only teaches several specific allele sizes which are associated with bipolar mood disorder.*" Final Office Action, bridging paragraph, pages 11 and 12, emphasis added. Thus, the Final Office Action acknowledged that the specification teaches several specific allele sizes (polymorphisms) that are associated with BP. Appellants submit that a description of "only several" polymorphisms satisfies the written description requirement of 35 U.S.C.§112, first paragraph.

In view of the fact that the instant specification teaches a number of specific polymorphisms that were shown, by analysis of both a pedigree and a population of unrelated individuals, to be associated with BP, the specification, and thus claims 1-12 and 25-27, meet the written description requirement of 35 U.S.C.§112, first paragraph.

II. WHETHER THE INVENTION IS ENABLED UNDER 35 U.S.C.§112, FIRST PARAGRAPH

The Final Office Action stated that:

(1) the specification does not reasonably provide enablement for a method of detecting an increased susceptibility to bipolar mood disorder (BP) by detecting a polymorphism between and inclusive of SAVA5 and ga203 or any of the other recited markers;

(2) the art teaches that while a linkage has been shown between several different chromosomal regions and BP, a susceptibility locus for this disease has yet to be identified; and

(3) the teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with BP without undue experimentation because of the extensive amount of unpredictability in this field as shown by the analysis of the prior art and because the specification has not provided evidence that would allow the skilled artisan to predict where and what the BP susceptibility polymorphisms will be.

Comments regarding the instant invention as claimed

The claims recite a method for detecting an increased susceptibility to BP in an individual, a method for detecting the presence of a BP susceptibility DNA polymorphism, a method of genetically diagnosing BP, and a method of confirming a phenotypic diagnosis of BP. The methods generally involve analyzing a sample of DNA from an individual for the presence of a polymorphism associated with BP on the short arm of chromosome 18p between SAVA5 and ga203. *The polymorphism is **associated** with BP; the polymorphism is not necessarily the **cause** of BP.*

The following analogy may prove instructive. A person who is carrying matches in his pocket is likely a smoker. The matches in the person's pocket are associated with smoking; however, they do not cause smoking. The likelihood that a person is a smoker is indicated by the presence of the matches in the person's pocket. In an analogous way, the claims recite polymorphisms associated with BP, not polymorphisms that cause BP.

The instant specification provides a description of a number of polymorphisms that were shown, both in a pedigree analysis, and in an analysis of a population of unrelated individuals, to be associated with BP. These polymorphisms are found in a narrow interval on the short arm of chromosome 18, between SAVA5

and ga203. Furthermore, during prosecution, Applicants provided a Declaration of Alison McInnes which showed that several additional polymorphisms were found in this region that also associate with BP. While the specification provides sufficient enablement, and the Declaration of Alison McInnes was further demonstration of this fact, Appellants also provide herewith a publication which shows that those in the field also found a polymorphism in a gene that is in the same narrow interval (i.e., between SAVA5 and ga203), and that is associated with BP. The evidence presented more than adequately demonstrates that the instant specification is enabling for the full scope of the claims.

The specification provides ample description of polymorphisms associated with BP, and further provides a detailed description of how to determine whether a given polymorphism is associated with BP.

Applicants have described in great detail:

(1) Identification of a narrow interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP. This identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification. Specification, page 16, line 12 to page 25, line 10.

(2) Identification of polymorphisms, e.g., allele 154 at D18S59, a microsatellite marker polymorphism that associates with BP; and allele 271 at D18S476, another microsatellite marker polymorphism that associates with BP. Specification, page 24, lines 10-29. These polymorphisms associated with BP both in the pedigree and in the population of unrelated individuals. Thus, a number of polymorphisms were identified that are unequivocally associated with BP.

(3) How additional polymorphisms within the defined, narrow region can be identified in other BP patients. Specification, page 27, line 22 to page 29, line 29.

(4) How individuals whose BP status is unknown ("test individuals") can be analyzed for the presence of a polymorphism known to be associated with BP. Specification, page 29, lines 23-29.

The Office Action stated that the specification is enabling for a method of detecting an increased susceptibility for bipolar mood disorder by performing a pedigree analysis for the individual's family, and

analyzing the DNA from family members for linkage of markers on the short arm of chromosome 18 between and inclusive of SAVA5 and ga203, D18S1140 and ga203, SAVA5 and W3422, D18S1140 and W3422, D18S1140 and ta201, and D18S59 and ta201.

However, as shown in the Examples, Applicants demonstrated unequivocally that a number of polymorphisms, including, e.g., allele 154 at D18S59, and allele 271 at D18S476, are associated with BP in *both pedigree analysis and in an analysis of a population of unrelated individuals*. Thus, the claims are enabled for performing an analysis on a sample of DNA from a test individual, and need not be limited to performing a pedigree analysis.

The final Office Action stated that the specification has not identified polymorphisms in the region between SAVA5 and ga203 that can be detected in any individual and which are generally associated with BP. However, as discussed above, the finding that the above-discussed polymorphisms were identified in a population of unrelated individuals indicates that such polymorphisms are generally associated with BP.

The final Office Action further stated that the markers described in the specification are not in and of themselves BP susceptibility polymorphisms because these markers are polymorphic sequences which are found throughout the genome and are not specific to this described region of chromosome 18. This is not correct. While it is true that microsatellite markers in general are found throughout the genome, the specific microsatellite markers identified in the present application are not found throughout the genome.

The whole reason for using microsatellite markers is that they are unique genetic addresses in the genome. While microsatellite markers are widespread throughout the genome, the sequences flanking each microsatellite marker are unique. Therefore, as described in the specification, using primer pairs that are specific for these unique flanking sequences, each microsatellite marker can be individually identified, as each set of primers describes absolutely unique sequences flanking the repeat. Therefore, each

microsatellite marker provides a unique genomic address. Variations in allele sizes of microsatellite markers are polymorphisms that are easily identifiable.

The specific microsatellite markers identified in the instant application, e.g., D18S59 and D18S476, are found only in the narrow region between SAVA5 and ga203, and the specific allele sizes of D18S59 and D18S476 of 154 and 271 bp, respectively, were shown to be associated with BP.

Applicants have described in detail how to identify additional polymorphisms associated with BP.

As noted above, Applicants have described in great detail: (1) Identification of a small interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP, which identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification; (2) Identification of polymorphisms, e.g., allele 154 at D18S59, and allele 271 at D18S476, which associate with BP (see, e.g., Table I, page 24); and (3) How additional polymorphisms within the narrow interval can be identified in other BP patients.

Those skilled in the art can thus readily identify, using the guidance in the specification, a polymorphism(s) within the identified region that associate with BP. The specification provides both a narrow region that is associated with BP (namely, the region on chromosome 18 between SAVA5 and ga203) as well as polymorphisms within this region that associate with BP. Thus, the specification is indeed enabling for a method of detecting the presence of a BP susceptibility polymorphism in an individual.

The Declaration of Alison McInnes provided further evidence of the fact that those skilled in the art could identify polymorphisms in the SAVA5-ga203 region that are associated with BP.

Given the guidance provided in the specification, those skilled in the art could readily determine whether a given polymorphism within the region recited in the claims is associated with BP. The Declaration of Alison McInnes attests to this fact. The Declaration of Alison McInnes was provided along with the amendment, filed October 10, 2001, responsive to the Final Office Action. A copy of this Declaration is provided herewith for convenience. The Declaration shows that, using techniques

described in the specification, **at least five polymorphisms**, including single nucleotide polymorphisms (SNP), in the narrow interval on chromosome 18p described in the application, are associated with BP. Thus, in addition to the polymorphisms already identified in the patent application, and using the guidance provided in the application, several additional polymorphisms were identified that are associated with BP.

Further evidence that those skilled in the art can identify polymorphisms in the SAVA5-ga203 region that are associated with BP.

Given the guidance in the instant specification, those in the field could readily identify polymorphisms associated with BP. Further evidence for this fact is provided in PCT publication WO 99/47535, provided herewith as Exhibit 1. This evidence was not provided earlier, as it was believed that the arguments provided in the various amendments, as well as the Declaration of Alison McInnes, as discussed above, provided ample evidence of enablement.

WO 99/47535 describes a gene, designated *HKNG1*. This gene is located in the region between SAVA5 and ga203. WO 99/47535 describes mutations in the *HKNG1* gene that are associated with BP. WO 99/47535 provides further evidence for the fact that those skilled in the art could, given the guidance in the instant specification, identify polymorphisms within the SAVA5-ga203 interval that are associated with BP. Thus, WO 99/47535 provides further evidence that the instant specification is enabling.

WO 99/47535 published on September 23, 1999, and lists Nelson B. Freimer as an inventor. (Nelson B. Freimer is also an inventor on the instant application.) WO 99/47535 presents evidence that mutations within a gene, designated *HKNG1*, are associated with BP. WO 99/47535, page 6, lines 23-27. (Note that in WO 99/47535, BP is referred to as "bipolar affective disorder" or "BAD"). WO 99/47535 discusses the use of linkage disequilibrium studies (as described in the instant specification). WO 99/47535, page 101, line15-21. WO 99/47535 used the information provided in the instant specification, which identified a narrow interval between SAVA5-and ga203 as associated with BP. WO 99/47535, page 103, lines 5-11. WO 99/47535 describes performing high resolution physical mapping and further narrowing of the interval (using linkage disequilibrium). WO 99/47535, page 103, line 12-page 104, line 30. These techniques are also described in the instant specification, and many were known

to those skilled in the art as of the filing date of the instant specification. Finally, WO 99/47535 describes the *HKNG1* gene, and mutations in the *HKNG1* gene that are associated with BP. WO 99/47535, page 109, line 17 to page 110, line 2. The *HKNG1* gene is *CLUL1* (Clusterin-like retinal protein 1) in the public database. The *HKNG1* gene also contains D18S59 and other polymorphisms shown to be associated with BP, i.e., D18S59 and other BP-associated polymorphisms are in *HKNG1* introns and 3' untranslated region.

Accordingly, using the techniques described in the specification, others in the field could identify mutations associated with BP, including mutations in genes.

The cited art does not support a conclusion of non-enablement of the instant claims.

The final Office Action cited various publications in support of the contention that the teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar (BP) susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field. The cited art are Stine et al. ((1995) *Am. J. Hum. Genet.* 57:1384-1394); McInnes et al. ((1996) *Proc. Natl. Acad. Sci.* 93:13060-13065 ("the McInnes Reference"); Esterling et al. ((1997) *Molec. Psychiatry* 2:501-504); Ewald et al. ((1997) *Psychiatric Genetics* 7:1-12); Gershon et al. ((1998) *Neuropsychopharmacology* 18:233-242); and Nöthen et al. ((1999) *Molec. Psychiatry* 4:76-84").

The present invention is based on studies that differed from previous studies in several respects. These differences can account for the failure of others, and the success of the present inventors, in finding polymorphisms associated with BP. These differences are can be summarized as follows: (1) others reported **pedigree-based studies**, while the present invention relates to a **population-based study**; (2) others did not use **linkage disequilibrium analysis**; and (3) others **included irrelevant phenotypes**, while the present study **excluded irrelevant phenotypes**. These differences were described in detail in the response to the June 28, 2000 Office Action. *Since the cited studies could not have provided the*

kind of information that the instant inventors were able to provide, none of the cited art supports a conclusion of non-enablement of the instant claims.

The McInnes reference: The McInnes reference **analyzed extended families, and used linkage analysis.** The Office Action stated that the McInnes reference teaches that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for any psychiatric disorder, and further stated that the McInnes reference teaches that the second and third stages in their process were delineating clear candidate regions so as to identify genes associated with BP. *The present invention as claimed is not directed to genes associated with bipolar mood disorder*. Instead, the claimed invention is directed to methods involving analyzing a DNA sample for the presence of a DNA polymorphism associated with BP. Furthermore, the claimed invention does not relate to establishing a *cause* of BP; instead, the claimed invention involves analyzing a DNA sample for polymorphisms *associated* with BP. It is further noted that the McInnes reference did not use linkage disequilibrium analysis of a large number of unrelated individuals, as in the present study, and thus cannot be used to show lack of enablement of the instant invention as claimed. **Thus, the McInnes reference describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.**

Stine: The Office Action stated that Stine "showed evidence of linkage between bipolar disorder and markers on the short arm of chromosome 18, i.e., 18p including marker D18S59 (table 1)." Office Action, page 3. This latter statement is inaccurate, as discussed in the response to the July 28, 1999 Office Action. A careful reading of Stine's Table 1, as well as the text of Stine, clearly show that Stine found no linkage between BP and D18S59. The Office Action further stated that Stine "acknowledged that the number of loci and their precise location require further study." Office Action, page 3. Stine conducted a study of 28 nuclear families. These families were unrelated to one another, and therefore the data obtained were not amenable to linkage disequilibrium analysis, as was done in the present invention. **Thus, Stine describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.** The fact that Stine found no linkage of D18S59 with BP only

further emphasizes the inadequacies of the Stine study and the superior nature of the study of the present application.

Esterling: The Office Action stated that Esterling constructed a high resolution map of 18p11.2 which they state contains a potential BP susceptibility locus, and that despite having the map, no specific polymorphisms or loci have been identified as a bipolar susceptibility locus. Esterling merely describes development of a high-resolution map of the 18p11.2 region. Esterling does not describe any attempts whatsoever to identify a polymorphism associated with BP in the region studied. Accordingly, the relevance of Esterling's disclosure to the question of enablement of the instant specification is unclear.

Ewald: The Office Action stated that Ewald teaches that while chromosome 18 is one of the most promising chromosomes to contain a bipolar susceptibility locus, the research is still considered a search for susceptiblity genes. First, Ewald reports on the results of a study of Danish families. As with the Stine study, these studies were conducted with isolated, unrelated families. Thus, the data were not amenable to the rigorous analysis to which the data presented in the instant application were subjected. **Accordingly, Ewald describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.** Second, *the present invention as claimed is not directed to specific genes associated with bipolar mood disorder*. Instead, all that is required in the present invention as claimed is that one be able to analyze a sample of DNA for a polymorphism associated with BP, said polymorphism being in the recited region of chromosome 18.

Gershon: The Office Action stated that Gershon teaches that scientists are yet a long way from demonstrating disease mutations in BP. Gershon here is referring to the identification of genes associated with BP. The title of Gershon's publication is "Closing in on genes for manic-depressive illness and schizophrenia." *The present invention as claimed is not directed to specific genes associated with bipolar mood disorder*. Instead, all that is required in the present invention as claimed is that one be able to analyze a sample of DNA for a polymorphism associated with BP, said polymorphism being in the recited region of chromosome 18.

Gershon summarizes several of the reports in the literature attempting to identify linkage of a chromosomal region with BP. Gershon, Table 1, page 236. Gershon states "*there is an uncomfortable number of nonreplications for the findings in Table 1.*" Gershon, page 236, column 1, first sentence of second full paragraph, emphasis added. Gershon further remarks, with regard to the studies cited in Table 1: "*There is very little statistical power to detect this sort of linkage in the sample sizes commonly used.*" Gershon, page 236, column 2, lines 7-8 of first incomplete paragraph, emphasis added. Thus, Gershon recognized the shortcomings of the work of others **and, as discussed in detail above, others have described pedigree-based studies, not a population-based study, and linkage disequilibrium analysis was not used.** Therefore, Gershon's critique cannot be fairly cited as a critique of the work of the claimed invention. The teaching of Gershon cannot be relied upon to support a conclusion of non-enablement of the instant invention as claimed.

Nöthen: The Office Action stated that Nöthen concluded as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may exist on chromosome 18, but does not provide a reasonable expectation as of yet that polymorphism in the region of 18p is associated with a bipolar susceptibility locus or what that locus will be. Nöthen reports on results of a study of 57 unrelated German families, and stated that the analysis revealed no robust evidence for linkage. This finding is not surprising in view of the foregoing discussion of the requirements for unequivocal linkage. As with the findings reported in Stine, Ewald, Esterling, and Gershon, the data in Nöthen were not amenable to linkage disequilibrium analysis. **Nöthen describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.**

In conclusion, the work described in Stine, Ewald, Esterling, Gershon, and Nöthen suffer from at least two drawbacks, as compared to the work of Applicants. These other studies used **pedigree-based studies,** sample sizes that were too small, and involved unrelated families. Because of the small sample sizes and lack of relatedness, the data were not amenable to rigorous statistical analysis. Thus, the failure of others in the field is merely a reflection of the fact that the systems analyzed by others are inadequate to support detection of DNA polymorphisms associated with susceptibility to developing BP. Indeed, as stated in the instant

specification, "earlier studies used largely uninformative markers and did not use stringent criteria for identifying affected individuals." Specification, page 4, lines 4-5.

The teachings in the specification provide the skilled artisan with a reasonable expectation that he will identify polymorphisms without undue experimentation.

The final Office Action stated that the teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with BP without undue experimentation because of the extensive amount of unpredictability in this field as shown by the analysis of the prior art and because the specification has not provided evidence that would allow the skilled artisan to predict where and what the BP susceptibility polymorphisms will be.

As discussed in detail above, the cited prior art does not support a conclusion of lack of enablement. Furthermore, as discussed above, the specification provides ample guidance for one of ordinary skill in the art to detect a polymorphism in the region of chromosome 18p between SAVA5 and ga203, and to determine whether the polymorphism is associated with BP.

The determination of whether a given polymorphism associates with BP was readily performed by those of ordinary skill in the art as of the filing date, given the guidance in the specification and the general knowledge in the art. The methods described in the specification were well known to those skilled in the art as of the filing date. At the time of filing, a number of methods were available to detect polymorphisms, including detection of microsatellilite alleles, and those skilled in the art were well aware of these methods. Linkage disequilibrium analysis to determine whether a given polymorphism is associated with BP is described in ample detail in the instant specification, including working examples. Specification, page 16, line 12 to page 25, line 10.

Applicants provided **working examples** of polymorphisms associated with BP, how such polymorphisms were detected, and how their association with BP was determined. Those skilled in the art could readily find additional polymorphisms in the region on chromosome 18 between SAVA5 and ga203, and

determine whether the additional polymorphisms associate with BP, by using the same techniques. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C.§112, first paragraph, is satisfied. *In re Fisher*, 166 USPQ 18 (CCPA 1970). Since the application discloses at least one method for detecting polymorphisms in the region of chromosome 18 between SAVA5 and ga203, and teaches how to determine whether any given polymorphism associates with BP, the claims satisfy the enablement requirement of 35 U.S.C.§112, first paragraph.

Thus, those skilled in the art, given the guidance in the specification and the general knowledge in the art, would reasonably expect to be able to identify additional polymorphisms within the region between SAVA5 and ga203, and to be able to determine whether such polymorphisms associate with BP. The level of experimentation required would not be undue, because the methods described in the specification were known as of the filing date, and because the specification provides ample guidance.

Conclusion

The specification provides ample description of polymorphisms associated with BP, and further provides a detailed description of how to determine whether a given polymorphism is associated with BP. The cited art does not support a conclusion of non-enablement of the instant claims. The teachings in the specification provide the skilled artisan with a reasonable expectation that he will identify polymorphisms without undue experimentation. In view of these facts, it is clear that claims 1-12 and 25-27 are supported by a disclosure that meets the enablement requirement of 35 U.S.C.§112, first paragraph.

SUMMARY

The instant specification provides ample written description and enablement for the claimed invention. The instant specification teaches a number of specific polymorphisms that were shown, by analysis of both a pedigree and a population of unrelated individuals, to be associated with BP. For this reason, and as further elaborated upon above, claims 1-12 and 25-27 meet the written description of 35 U.S.C.§112, first paragraph.

Claims 1-12 and 25-27 also meet the enablement requirement of 35 U.S.C.§112, first paragraph, because the specification provides ample description, including working examples, of how to identify polymorphisms in the region of chromosome 18 recited in the claims (i.e., between SAVA5 and ga203), and how to determine whether such polymorphisms are associated with BP.

RELIEF REQUESTED

Appellants respectfully request that the rejection of claims 1-12 and 25-27 under 35 U.S.C. §112, first paragraph be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

REQUEST FOR ORAL HEARING

Appellants request an oral hearing on this appeal, and enclose two additional copies of this Brief in connection therewith.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Jan. 10, 2002

By: _____
Paula A. Borden
Registration No. 42,344

Enclosures:
1) Appendix of Pending Claims
2) Copy of pages 31-32 of Laboratory Methods for the Detection of Mutations and Polymorphisms in DNA, (1997) G.R. Taylor, ed. CRC Press, filed with the amendment, filed March 17, 2000, responsive to the January 20, 2000 Office Action
3) Copy of Declaration of Alison McInnes, filed with the amendment, filed October 10, 2001, responsive to the Final Office Action
4) Exhibit 1: WO 99/47535

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APPENDIX OF PENDING CLAIMS

1. A method of detecting an increased susceptibility to bipolar mood disorder (BP) in an individual comprising:

analyzing a sample of DNA from a test individual for the presence of a DNA polymorphism associated with BP on the short arm of chromosome 18 between SAVA5 and ga203, wherein the presence in the test individual of a polymorphism associated with BP which is present on a disease chromosome indicates that the test individual has an increased susceptibility to develop BP.

2. The method of claim 1, wherein said DNA polymorphism is located on the short arm of chromosome 18 between and inclusive of D18S1140 and ga203.

3. The method of claim 1, wherein said DNA polymorphism is located on the short arm of chromosome 18 between and inclusive of SAVA5 and W3422.

4. The method of claim 1, wherein said DNA polymorphism is located on the short arm of chromosome 18 between and inclusive of D18S11 and W3422.

5. The method of claim 1, wherein said DNA polymorphism is located on the short arm of chromosome 18 between and inclusive of D18S1140 and at201.

6. The method of claim 1, wherein said DNA polymorphism is located on the short arm of chromosome 18 between and inclusive of D18S1140 and ta201.

7. The method of claim 1, wherein said DNA polymorphism is located on the short arm of chromosome 18 between and inclusive of D18S59 and ta201.

8. The method of claim 1, wherein said analyzing further comprises

a) analyzing DNA samples obtained from family members for the presence of said DNA polymorphism; and

b) correlating the presence or absence of the DNA polymorphism with a phenotypic diagnosis of bipolar mood disorder for said individual or for said family members, wherein a correlation is indicative of an increased susceptibility to develop BP.

9. A method for detecting the presence of a bipolar mood disorder (BP) susceptibility DNA polymorphism in an individual phenotypically diagnosed as having BP, the method comprising:

a) typing blood relatives of said individual for a DNA polymorphism located within a 500kb region of chromosome 18, wherein said region is located between and inclusive of SAVA5 and ga203; and

b) analyzing a DNA sample from said individual for the presence of said DNA polymorphism, wherein a sharing of said DNA polymorphism in said region between the individual and a blood relative who has been phenotypically diagnosed as having BP is an indication that the polymorphism is a BP susceptibility polymorphism.

10. A method of genetically diagnosing bipolar mood disorder in an individual comprising:

analyzing a DNA sample obtained from a test individual for the presence of a DNA polymorphism associated with bipolar mood disorder, wherein said DNA polymorphism is located within a 500 kb region of chromosome 18, wherein said region is located between and inclusive of SAVA5 and ga203, wherein the presence in the test individual of a polymorphism which is present on a disease chromosome indicates that the individual has bipolar mood disorder.

11. A method of confirming a phenotypic diagnosis of bipolar mood disorder in an individual comprising:

analyzing a DNA sample obtained from a test individual phenotypically diagnosed as having bipolar mood disorder for the presence of a DNA polymorphism associated with bipolar mood disorder, wherein said DNA polymorphism is located within a 500 kb region of chromosome 18, wherein said

region is located between and inclusive of SAVA5 and ga203, wherein the presence in the test individual of the polymorphism which is present on a disease chromosome confirms a phenotypic diagnosis of bipolar mood disorder.

12. The method of claim 10, wherein said individual has Spanish or Amerindian ancestry.

25. The method of claim 1, wherein the polymorphism is a polymorphic microsatellite marker.

26. The method of claim 25, wherein the polymorphism is a single nucleotide polymorphism.

27. A method of detecting the presence of a bipolar mood disorder susceptibility polymorphism in an individual comprising:

analyzing a sample of DNA from said individual for the presence of a DNA polymorphism on the short arm of chromosome 18 between SAVA5 and ga203; and

determining the frequency of the polymorphism on disease chromosomes and non-disease chromosomes, wherein an overrepresentation of the polymorphism on disease chromosomes indicates that the DNA polymorphism is associated with a form of bipolar mood disorder.

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PTO/SB/21 (08-00)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/976,560
Filing Date	November 24, 1997
First Named Inventor	FREIMER, NELSON B.
Group Art Unit	1655
Examiner Name	ARTHUR, L.
Total Number of Pages in This Submission	32 + 3 Exhibits (in triplicate)
Attorney Docket Number	UCAL142CON

ENCLOSURES (check all that apply)

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Documents
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) ____
- [ ] After Allowance Communication to Group
- [x] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) *(please identify below):*
  1) Exhibit 1
  2) 2 Previously Submitted Exhibits

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual Name	PAULA A. BORDEN, Reg. No. 42,344
Signature	
Date	January 10, 2002

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date: January 10, 2002.

Typed or printed name	Cindy Kim Hoang		
Signature		Date	January 10, 2002

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT	($) 710.00

Complete if Known	
Application Number	08/976,560
Filing Date	November 24, 1997
First Named Inventor	FREIMER, NELSON B.
Examiner Name	ARTHUR, L.
Group Art Unit	1655
Attorney Docket No.	UCAL142CON

METHOD OF PAYMENT

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit overpayments to:
   Deposit Account Number **50-0815**
   Deposit Account Name **Bozicevic, Field & Francis LLP**
   ☒ Charge Any Additional Fee Required Under 37 CFR 1.1 6 and 1.17
   ☐ Applicant Claims small entity status. See 37 CFR 1.27

2. ☐ **Payment Enclosed:**
   ☐ Check ☐ Credit Card ☐ Money Order ☐ Other

FEE CALCULATION

2. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	
				SUBTOTAL (1)	

1. EXTRA CLAIM FEES

	Extra Claims		Fee from below		Fee Paid
Total Claims 15 -20	=	x		=	
Indep. Claims 5-7	=	x		=	
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 **and over original patent**
				SUBTOTAL (2) $

***or number previously paid, if greater; For Reissues, see above.*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late filing fee or oath	
127	50	227	25	Surcharge – late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examination action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	**110.00**
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	320.00
121	280	221	140	Request for oral hearing	**280.00**
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	For each additional invention to be examined (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify)_____

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3) ($) 710.00**

SUBMITTED BY				Complete (*if applicable*)	
Name (Print/Type)	Paula A. Borden	*Registration No. (Attorney/Agent)*	42,344	*Telephone*	(650) 327-3400
Signature				*Date*	01/10/2002

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